Search Strategy

FILE 'MEDLINE' ENTERED AT 18:37:01 ON 22 JUN 2003

		E	ZAGURY D/AU
L1	135	S	E3
L2	10	S	L1 AND TAT
L3	131782	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L4	5213	S	L3 AND (DISEASE AND PROGRESSION)
L5	71	S	L4 AND (PREDICTOR? AND OUTCOME)
L6	9	S	L5 AND (P24)
L7	8	S	L5 AND (P24 ANTIGEN OR P24 ANTIGENEMIA OR P24 ANTIGENAEMIA)
L8	0	S	L7 NOT L6
L9	235	S	L4 AND (P24 ANTIGEN OR P24 ANTIGENEMIA OR P24 ANTIGENAEMIA)
L10	227	S	L9 NOT L6
L11	103	S	L10 AND MARKER?
L12	83	S	L11 AND (DISEASE PROGRESSION OR CLINICAL OUTCOME)
L13	1	S	L5 AND TAT
L14	1	S	L12 AND TAT
L15	85	S	L4 AND TAT
L16	56	S	L15 AND (DISEASE PROGRESSION OR CLINICAL OUTCOME)

FILE 'USPATFULL' ENTERED AT 19:45:03 ON 22 JUN 2003

		E	ZAGURY DANIEL/IN
L17	6	S	E3
L18	24988	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L19	5432	S	L18 AND (DISEASE AND PROGRESSION)
L20	127	S	L19 AND (PREDICTOR? AND OUTCOME)
L21	25	S	L20 AND TAT
L22	0	S	L20 AND TAT/CLM
L23	6	S	L20 AND (P24 ANTIGEN?)

FILE 'WPIDS' ENTERED AT 19:51:03 ON 22 JUN 2003

		E	ZAGURY D/IN
L24	9	S	E3
L25	15446	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L26	161	S	L25 AND (DISEASE AND PROGRESSION)
L27	0	S	L26 AND (PREDICTOR? AND OUTCOME)
L28	21	S	L26 AND (MARKER?)
L29	1	S	L26 AND (P24 ANTIGEN?)
L30	9	S	L26 AND TAT

L2 ANSWER 6 OF 10 MEDLINE
1999194245 Document Number: 99194245. PubMed ID: 10096581. Tat toxoid as a component of a preventive vaccine in seronegative subjects. Gringeri A; Santagostino E; Muca-Perja M; Le Buanec H; Bizzini B; Lachgar A; Zagury J F; Rappaport J; Burny A; Gallo R C; Zagury D. (A. Bianchi Bonomi Hemophilia and Thrombosis Center, Istituto di Ricovero e Cura a Carattere Scientifico Maggiore Hospital and State University of Milan, Italy.. hemophilia_ctr@polic.cilea.it) . JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY, (1999 Apr 1) 20 (4) 371-5. Journal code: 9501482. ISSN: 1077-9450. Pub. country: United States. Language: English.

AB Because administration of Tat protein, the HIV-1 toxin that induces immunosuppression and apoptosis, may be deleterious to the host immune system, a chemically inactivated but nonetheless immunogenic Tat preparation, Tat toxoid, was used to immunize seronegative individuals against Tat. In an open, controlled, phase I clinical trial, Tat toxoid turned out to be safe, well tolerated, and able to trigger a specific immune reaction. In particular, a threefold to more than 10-fold increase of circulating antibodies directed against the native Tat was observed after immunization in all of 5 immunized study subjects, together with a positive reaction to delayed-type hypersensitivity (DTH) skin test with Tat toxoid in vivo and increased lymphoproliferative response to native Tat in vitro. Persistent (> or =1 year) high levels of circulating anti-Tat antibodies could prevent the Tat-induced immune suppression and, following HIV-1 exposure, allow the anti-HIV-1 cellular immune response, with its early release of protective beta-chemokines, to occur leading to an increase of host resistance, that is, protection.

L2 ANSWER 5 OF 10 MEDLINE
1999211157 Document Number: 99211157. PubMed ID: 10195253. Antibodies to the HIV-1 Tat protein correlated with nonprogression to AIDS: a rationale for the use of Tat toxoid as an HIV-1 vaccine. Zagury J F; Sill A; Blattner W; Lachgar A; Le Buanec H; Richardson M; Rappaport J; Hendel H; Bizzini B; Gringeri A; Carcagno M; Criscuolo M; Burny A; Gallo R C; Zagury D. (Universite Pierre et Marie Curie, Paris, France.) JOURNAL OF HUMAN VIROLOGY, (1998 May-Jun) 1 (4) 282-92. Journal code: 9805755. ISSN: 1090-9508. Pub. country: United States. Language: English.

AB OBJECTIVES: To investigate which immune parameters, such as antibodies against HIV-1 specificities, or viral parameters, such as p24 antigenemia, are predictive of disease progression. STUDY DESIGN: We performed studies on serum collected from individuals exhibiting two extremes of disease evolution--67 fast progressors (FP) and 182 nonprogressors (NP)--at their enrollment. After a 1- to 2-year clinical follow-up of 104 nonprogressors after their enrollment, we could determine the best serologic predictors for disease progression. METHODS: We investigated levels of antibodies to tetanus toxoid and to HIV antigens including Env, Gag, Nef, and Tat proteins, as well as p24 antigenemia, viremia, CD4 cell count, and interferon-alpha (IFN-alpha) titers in FPs and NPs, and we correlated these data with clinical and biologic signs of progression. RESULTS: p24 Antigenemia, a marker of viral replication, and anti-Tat antibodies were highly and inversely correlated in both groups ($P < .001$). Furthermore, anti-p24 antibodies and low serum IFN-alpha levels were correlated to the NP versus the FP cohort. Finally, among NPs, only antibodies to Tat and not to the other HIV specificities (Env, Nef, Gag) were significantly predictive of clinical stability during their follow-up. CONCLUSION: Antibodies toward HIV-1 Tat, which are

inversely correlated to p24 antigenemia, appear as a critical marker for a lack of disease progression. This study strongly suggests that rising anti-Tat antibodies through active immunization may be beneficial in AIDS vaccine development to control viral replication.

L2 ANSWER 4 OF 10 MEDLINE
1999211158 Document Number: 99211158. PubMed ID: 10195254. Safety and immunogenicity of HIV-1 Tat toxoid in immunocompromised HIV-1-infected patients. Gringeri A; Santagostino E; Muca-Perja M; Mannucci P M; Zagury J F; Bizzini B; Lachgar A; Carcagno M; Rappaport J; Criscuolo M; Blattner W; Burny A; Gallo R C; Zagury D. (Hemophilia and Thrombosis Center Angelo Bianchi Bonomi, IRCCS Maggiore Hospital, Milan, Italy.. hemophilia_ctr@polic.cilea.it) . JOURNAL OF HUMAN VIROLOGY, (1998 May-Jun) 1 (4) 293-8. Journal code: 9805755. ISSN: 1090-9508. Pub. country: United States. Language: English.

AB OBJECTIVES: To antagonize the deleterious effects of the HIV-1 toxin extracellular Tat on uninfected immune cells, we developed a new strategy of anti-HIV-1 vaccine using an inactivated but immunogenic Tat (Tat toxoid). Tat-toxoid has been assayed for safety and immunogenicity in seropositive patients. METHOD: The phase I vaccine clinical trial testing Tat toxoid preparation in Seppic Isa 51 oil adjuvant was performed on 14 HIV-1-infected asymptomatic although biologically immunocompromised individuals (500-200 CD4+ cells/mm3). RESULTS: Following as many as 8 injections, no clinical defects were observed. All patients exhibited an antibody (Ab) response to Tat, and some had cell-mediated immunity (CMI) as evaluated by skin test in vivo and T-cell proliferation in vitro. CONCLUSION: These results provide initial evidence of safety and potency of Tat toxoid vaccination in HIV-1-infected individuals.

L6 ANSWER 7 OF 9 MEDLINE
94280701 Document Number: 94280701. PubMed ID: 7912084. Quantification of HIV-1 virus load under zidovudine therapy in patients with symptomatic HIV infection: relation to disease progression. Molina J M; Ferchal F; Chevret S; Barateau V; Poirot C; Morinet F; Modai J. (Department of Infectious Diseases, Hopital Saint-Louis, Paris, France.) AIDS, (1994 Jan) 8 (1) 27-33. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: To measure changes in HIV-1 virus load following zidovudine therapy, and to investigate the relationship between these changes and clinical progression. DESIGN: Prospective study of 18 symptomatic, zidovudine-naive patients, with CD4 count < 350 x 10(6)/l. METHODS: The following parameters were measured at each visit, before zidovudine therapy, after 1 month of therapy, and every 3 months thereafter. HIV-1 virus load in peripheral blood was determined by serum immune complex-dissociated HIV-1 p24 antigen (ICD-p24 Ag), quantitative plasma and cellular viraemia. A virologic response under zidovudine was defined as > 50% decrease in ICD-p24 Ag levels or > 1 log10 decrease in plasma or cellular viraemia titres from baseline values. CD4 and CD8 cell counts, and beta 2-microglobulin levels were also measured. Disease progression was defined as the time to a new AIDS-defining event or death. RESULTS: At enrolment, 13 out of 18 (72%) patients had positive ICD-p24 Ag and positive plasma viraemia, with a mean of 44 median tissue culture infective dose (TCID50) per ml; all patients had positive cellular viraemia with a mean TCID50 of 230 per 10(6)/l cells. Median CD4 cell count was 43 x 10(6)/l. Ten patients developed a new AIDS-defining event and eight died during a median follow-up of 15 months on zidovudine. Baseline prognostic markers for development of a new

AIDS-defining event included ICD-p24 Ag, CD4 and CD8 cell counts, but only CD4 cell count remained predictive on multivariate analysis (P = 0.003). When each laboratory marker was analysed as a time-dependent covariate, only CD4 (P = 0.002) and CD8 (P = 0.001) cell counts predicted the occurrence of a new AIDS-defining event. Eight out of 13 (61.5%) patients had an ICD-p24 Ag response, and seven out of 13 (54%) a plasma viraemia response, but only cellular viraemia responders (five out of 18; 28%) had a 5.6-fold decrease in their risk of developing an AIDS-defining event (90% confidence interval, 1-33; P = 0.05). None of these markers correlated with survival. CONCLUSIONS: **Plasma viraemia and ICD-p24 Ag, while providing useful short-term markers of zidovudine antiviral activity in vivo, do not correlate with disease progression in patients with advanced HIV infection. CD4 cell count remained the best initial and time-dependent predictor for development of new AIDS-defining events. Interestingly, a high CD8 cell count and a decrease in cellular viraemia titres also appear to be predictive of improved clinical outcome in this population.**

L6 ANSWER 5 OF 9 MEDLINE

95162793 Document Number: 95162793. PubMed ID: 7859138. Serum beta 2-microglobulin and prediction of progression to AIDS in HIV-infected injection drug users. Zabay J M; Sempere J M; Benito J M; Gonzalez B; Obregon E; Diez J; Fernandez-Cruz E. (Department of Immunology, University General Hospital Gregorio Maranon, Complutense University, Madrid, Spain.) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY, (1995 Mar 1) 8 (3) 266-72. Journal code: 9501482. ISSN: 1077-9450. Pub. country: United States. Language: English.

AB Several immunological and serological variables have become established in recent studies as valuable markers to identify human immunodeficiency virus (HIV)-positive individuals at the highest risk for rapid disease progression. These studies have been performed mainly in cohorts of homosexual men. In this study, we assessed the usefulness of CD4 lymphocyte count, serum beta 2-microglobulin concentration, and the presence of p24 antigen as predictors of AIDS in a cohort of 130 HIV-positive injection drug users (IDUs) followed-up for 1 to 67 months. Progression to AIDS was most strongly associated with reduced absolute numbers of CD4+ lymphocytes at baseline, but increases in beta 2-microglobulin levels at baseline were an independent predictor of outcome. After stratification by baseline CD4 count, beta 2-microglobulin concentration added significant prognostic information to CD4 count among IDUs with > 500/mm3 CD4 cells (Breslow statistic value, 5.84, p = 0.01). Thus among seropositive IDUs with normal CD4 counts, increases in beta 2-microglobulin may be used as an early marker of individuals with higher risk of progression to AIDS, who may benefit from more intensive laboratory monitoring or clinical management.

L6 ANSWER 4 OF 9 MEDLINE

95221985 Document Number: 95221985. PubMed ID: 7706807. Predictors for non- and slow progression in human immunodeficiency virus (HIV) type 1 infection: low viral RNA copy numbers in serum and maintenance of high HIV-1 p24-specific but not V3-specific antibody levels. Hogervorst E; Jurriaans S; de Wolf F; van Wijk A; Wiersma A; Valk M; Roos M; van Gemen B; Coutinho R; Miedema F; +. (Human Retrovirus Laboratory, University of Amsterdam, Netherlands.) JOURNAL OF INFECTIOUS

DISEASES, (1995 Apr) 171 (4) 811-21. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB To gain insight into determinants that define the duration of the asymptomatic period preceding AIDS, groups of long-term asymptomatic (LTA) person (> 7 years of follow-up) and slow and rapid progressors of human immunodeficiency virus infection were studied. LTAs had no clinical manifestations of AIDS or immunologic abnormalities in 7 years of follow-up. RNA copy numbers, gag- and env-specific, and neutralizing antibody titers in serum were determined 1 and 5 years after seroconversion or entry into the cohort. Early in infection, before immunologic markers or clinical manifestations allowed group discrimination, subjects who were later classified as LTAs had significantly less serum viral RNA than progressors. No significant increase in virus load was found in progressors, indicating that the initial load defines clinical outcome. In **slow progressors, high virus load was associated with high p24-specific antibody titers, suggesting that delay of clinical manifestations of AIDS may be related to the presence of high levels of p24-specific but not V3-specific antibodies.**

L12 ANSWER 51 OF 83 MEDLINE
95118533 Document Number: 95118533. PubMed ID: 7529507. Evaluation of proviral copy number and plasma RNA level as early indicators of progression in HIV-1 infection: correlation with virological and immunological markers of disease.
Verhofstede C; Reniers S; Van Wanzeele F; Plum J. (Department of Clinical Chemistry, Microbiology and Immunology, University Hospital, Gent, Belgium.) AIDS, (1994 Oct) 8 (10) 1421-7. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: We compared the proviral DNA level in peripheral blood mononuclear cells (PBMC), viral RNA level in plasma, presence of p24 antigen in serum, viral phenotype, and results of immunological markers of HIV-1 disease.
METHODS: Consecutive samples of 62 HIV-1-infected patients, representing all stages of disease were tested for proviral DNA in PBMC and viral RNA in plasma using a semi-quantitative limiting dilution polymerase chain reaction (PCR). The presence of a syncytium-inducing (SI) phenotype was assessed after direct cocultivation of patient PBMC with MT-2 cells. Results of the quantitative PCR and the MT-2 coculture were correlated with the clinical stage of the disease, with the number of CD4+ T cells, and with the results of other virological and immunological markers, such as the level of p24 antigen, beta 2-microglobulin (beta 2M) and neopterin. RESULTS: Significant differences were observed between the results for asymptomatic and symptomatic patients for all markers under study. In the group of asymptomatic patients with a CD4+ T-cell count > 200 x 10(6)/l, patients with high amounts of proviral DNA had significantly higher amounts of beta 2M, neopterin and viral RNA, they were more frequently p24 antigen-positive and harboured more frequently SI strains than patients with low amounts of proviral DNA. A good correlation between the proviral DNA and the viral RNA levels was observed. Significant changes of viral RNA but not proviral DNA levels were observed after initiation of therapy or when therapy failed. CONCLUSIONS: We demonstrated the relationship between high proviral DNA level in PBMC, high viral load in plasma, elevated beta-2M and neopterin concentrations in serum, and the presence of p24 antigen in serum in a group of asymptomatic patients with a CD4+ T-cell count > 200 x 10(6)/l. We suggest the possible usefulness of

proviral load as an early indicator of disease progression. The presence of SI strains is highly correlated with disease; however, SI strains were detected in only 46% of symptomatic patients. It also appeared that the measurement of viral RNA levels is a useful marker for therapy monitoring.

L12 ANSWER 52 OF 83 MEDLINE
95105558 Document Number: 95105558. PubMed ID: 7806875. p24 antigenaemia in HIV-1 infected Brazilians correlates with other markers of disease progression.
Hofer C B; Pinto M E; Zajdenverg R; Schechter M. (Programa SIDA/AIDS, Hospital Universitario Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Brazil.) JOURNAL OF INFECTION, (1994 Sep) 29 (2) 129-31. Journal code: 7908424. ISSN: 0163-4453. Pub. country: ENGLAND: United Kingdom. Language: English.

L12 ANSWER 55 OF 83 MEDLINE
95014929 Document Number: 95014929. PubMed ID: 7929756. Quantification of human immunodeficiency virus in plasma by RNA PCR, viral culture, and p24 antigen detection. Van Kerckhoven I; Fransen K; Peeters M; De Beenhouwer H; Piot P; van der Groen G. (Department of Infection and Immunity, Institute of Tropical Medicine, Antwerp, Belgium.) JOURNAL OF CLINICAL MICROBIOLOGY, (1994 Jul) 32 (7) 1669-73. Journal code: 7505564. ISSN: 0095-1137. Pub. country: United States. Language: English.

AB A semiquantitative PCR technique for detecting human immunodeficiency virus type 1 (HIV-1) RNA in plasma was compared with quantitative viral culture and p24 antigen detection in plasma. Ninety-three samples from 20 symptomatic, 10 asymptomatic, and 10 seronegative individuals were tested. For most of the seropositive patients, consecutives samples were examined. Viral RNA was extracted from plasma by the method described by Boom et al. (R. Boom, C.J. A. Sol, M. M. M. Salimans, C.L. Jansen, P. M. E. Wertheim-van Dillen, and J. van der Noordaa, J. Clin. Microbiol. 28:495-503, 1990). The RNA PCR was the most sensitive method (100 and 74% sensitivity for symptomatic and asymptomatic patients, respectively) and produced less divergent results with the consecutive samples from individual patients compared with the other techniques. All samples positive by viral culture or p24 antigen assay were also positive in the RNA PCR. For each of the three assays, the number of positive results obtained correlated with the disease stage. The estimated mean number of HIV-1 RNA copies was significantly higher in symptomatic patients (22,750 copies per ml) than in asymptomatic patients (1,820 copies per ml). It was also higher in samples positive for viral culture than in culture-negative samples. No close correlation was found between the amount of HIV-1 RNA and the amount of p24 antigen or the titer of infectious virus in plasma or between this titer and the level of p24 antigen. The plasma RNA PCR may be a useful additional marker of disease progression and may be valuable for monitoring the effects of antiviral therapy.

L12 ANSWER 57 OF 83 MEDLINE
94365771 Document Number: 94365771. PubMed ID: 7916049. Correlation between surrogate markers, viral load, and disease progression in HIV-1 infection. Lafeuillade A; Tamalet C; Pellegrino P; de Micco P; Vignoli C; Quilichini R. (Department of Infectious Diseases, Chalucet Hospital, Toulon, France.) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, (1994 Oct) 7 (10) 1028-33. Journal code: 8812597. ISSN: 0894-9255. Pub. country: United States. Language:

English.

AB Surrogate markers generally used for observation of patients infected with human immunodeficiency virus (HIV) and their plasma and cellular viral load were assayed in a series of 40 patients before initiation of zidovudine therapy. Plasma viremia was positive in 62.5% of patients and was statistically correlated with clinical stage, CD4+ T cell count, CD8+ T cell count, beta 2-microglobulin level, neopterin level, and immunoglobulin A level. Cellular viremia was positive in 95% of patients and was correlated with clinical stage, CD4+ T cell count, beta 2-microglobulin, neopterin levels, and disease progression during the following months. **A discordance was found between p24 antigenemia, even after acid dissociation of immune complexes, and plasma viremia. In fact, p24 antigenemia was correlated with only biological markers of immune activation as beta 2-microglobulin and neopterin levels. The measurement of anti-p24 antibodies did not appear discriminative in our staging.** Plasma viremia, like CD4+ T cell count, reflects the patient's status at the time of assessment. Cellular viremia could be more informative for the prediction of future clinical progression.

L12 ANSWER 63 OF 83 MEDLINE
93228885 Document Number: 93228885. PubMed ID: 8097095. Serum levels of soluble CD8, neopterin, beta 2-microglobulin and p24 antigen as indicators of disease progression in children with AIDS on zidovudine therapy. Siller L; Martin N L; Kostuchenko P; Beckett L; Rautonen J; Cheng S C; Wara D W. (Department of Pediatrics, University of California, San Francisco.) AIDS, (1993 Mar) 7 (3) 369-73. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: To test the hypothesis that serum levels of soluble markers in children change after initiation of zidovudine therapy and that the extent and pattern of these longitudinal changes correlates with clinical outcome. PATIENTS AND METHODS: We measured serum levels of soluble CD8, neopterin, beta 2-microglobulin (beta 2M), and p24 antigen, and CD4 cell counts, before the initiation of zidovudine therapy and at 12, 24 and 48 weeks of treatment in 24 HIV-1-infected children (Centers for Disease Control classification P2) and 15 controls. RESULTS: Soluble CD8 levels were elevated before therapy in 70% of the infected children; subsequent decreases were associated with lower risk of disease progression. The mean serum neopterin level before treatment was elevated in infected children; decreases in neopterin levels marginally reflected improved or stable clinical status. Serum beta 2M levels and CD4+ cell counts were not associated with clinical outcome. **Only 10 out of the 24 patients had detectable levels of serum p24 antigen before treatment; again, the amount of decline after initiation of therapy did not predict clinical outcome.** CONCLUSION: Decreasing levels of soluble CD8 and neopterin in HIV-1-infected children receiving zidovudine therapy might reflect a good response to treatment and a slowing of disease progression.

L12 ANSWER 70 OF 83 MEDLINE
93039866 Document Number: 93039866. PubMed ID: 1418778. The effect of treatment with zidovudine with or without acyclovir on HIV p24 antigenaemia in patients with AIDS or AIDS-related complex. Pedersen C; Cooper D A; Brun-Vezinet F; Doherty R; Skinhoj P;

Perol Y; Luthy R; Leibowitch J; Habermehl K O; Varnier O E; +. (Hvidovre Hospital, Copenhagen, Denmark.) AIDS, (1992 Aug) 6 (8) 821-5. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: To evaluate changes in serum HIV p24-antigen levels in a subset of patients who participated in a European/Australian double-blind, placebo-controlled trial evaluating the efficacy of zidovudine (250 mg every 6 h) alone or in combination with acyclovir (800 mg every 6 h) in patients with AIDS, AIDS-related complex (ARC) or Kaposi's sarcoma (KS). DESIGN: Double-blind, placebo-controlled randomized clinical trial of less than or equal to 6 months' therapy. SETTING: Samples were obtained from patients attending teaching hospital outpatient clinics in seven European countries and Australia. SUBJECTS: One hundred and ninety-seven HIV-infected patients (60 with AIDS and 137 with ARC or KS). MAIN OUTCOME MEASURES: Serum HIV p24-antigen levels measured using the Abbott HIV solid-phase enzyme immunoassay. RESULTS: Of 76 ARC/KS patients who were initially HIV p24-antigen-positive, one out of 25 randomized to placebo, eight out of 23 to zidovudine and 11 out of 28 to the zidovudine/acyclovir combination became antigen-negative. The proportion of patients who became antigen-negative was significantly higher in both the zidovudine group (P = 0.016) and the zidovudine/acyclovir group (P = 0.004), compared with the placebo group. There were no statistical differences between the zidovudine and the zidovudine/acyclovir groups. During the trial p24-antigen levels in the zidovudine-treated patients reached their minimum after 4-8 weeks of therapy, and tended to increase gradually thereafter. **Disease progression occurred irrespective of whether p24-antigen levels declined during therapy. No association between p24-antigen responses to therapy and baseline disease stage, Karnofsky score or baseline CD4 cell count was detectable.** CONCLUSION: Acyclovir does not potentiate the effect of zidovudine on p24-antigen levels. Change in antigen level in response to antiviral therapy needs further investigation before it is used as a surrogate marker for clinical efficacy of antiviral therapy.

L12 ANSWER 25 OF 83 MEDLINE
1998049178 Document Number: 98049178. PubMed ID: 9389310. Use of virologic markers in clinical practice. Saag M S. (Department of Medicine, Division of Infectious Diseases, The University of Alabama at Birmingham, 35294-2050, USA.) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY, (1997) 16 Suppl 1 S3-13. Ref: 43. Journal code: 9501482. ISSN: 1077-9450. Pub. country: United States. Language: English.

AB A number of virologic and immunologic markers, including serum human immunodeficiency virus (HIV)-1 **p24 antigen levels**, quantitative HIV-1 microculture of plasma or peripheral blood mononuclear cells, and CD4 cell counts, have been used over the past decade to monitor progression of HIV infection. Although these markers are useful, **they have not provided a reliable means of assessing prognosis at all stages of the disease or response to antiretroviral treatment.** New molecular techniques are now available that measure viral load in HIV-infected patients by detecting and quantifying virion-associated RNA circulating in plasma. These plasma HIV-1 RNA levels appear to correlate with the clinical disease stage and reflect the response to antiretroviral treatment. Because recent

studies have demonstrated that **baseline plasma HIV-1 RNA levels and changes in these levels are predictive of clinical outcome**, it is strongly recommended that these markers be measured routinely and used as a guide in the management of all patients with HIV disease.

L12 ANSWER 29 OF 83 MEDLINE
97382866 Document Number: 97382866. PubMed ID: 9240857. Immunological and virological markers of disease progression in HIV-infected children. Munoz-Fernandez M A; Navarro J; Obregon E; Arias R A; Gurbindo M D; Sampelayo T H; Fernandez-Cruz E. (Division of Immunology, Hospital General Universitario Gregorio Maranun, Madrid, Spain.) ACTA PAEDIATRICA. SUPPLEMENT, (1997 Jun) 421 46-51. Journal code: 9315043. ISSN: 0803-5326. Pub. country: Norway. Language: English.

AB Polymerase chain reaction (PCR), virus culture and antigen detection assays are useful for early detection of vertically transmitted human immunodeficiency virus type 1 (HIV-1) infection in infants under 12 months of age. Sixty-four children born to HIV-1-seropositive mothers were evaluated. Thirteen children (20.3%) were repeatedly positive by PCR analysis. There was 100% concordance between the results obtained from PCR and culture assays. **Measurement of p24 antigen in serum was, in contrast, a less sensitive marker of HIV infection: only 5/13 infants had positive p24 antigen results.** We have investigated the relationship among the HIV-1 biological phenotype, replicative capacity of viral isolates, HIV RNA copy number in plasma, p24 antigenaemia, CD4 T lymphocyte counts and the clinical status in 13 HIV-infected infants. Six out of 13 HIV-1 isolates from these patients were classified as rapid/high and seven as slow/low. We have found a significantly positive correlation between the replication rate of HIV isolates and their capacity to induce syncytia in vitro. The HIV-1 isolates with rapid/high and syncytium-inducing phenotype, and isolates with slow/low and non-syncytium-inducing phenotype were obtained from infants who had HIV-1 RNA copy number ml(-1) plasma values of 27654-83520 and 1342-34321, respectively. Levels of HIV-1 RNA were measured in sequential plasma samples from three HIV -infected infants and their biological properties determined in vitro. Our findings indicate that infants who carried viruses with more cytophatic biological phenotype and who had higher viral RNA copy numbers in blood were more likely to have lower CD4+ T cell counts and more likely to develop full-blown AIDS.

L12 ANSWER 30 OF 83 MEDLINE
97363875 Document Number: 97363875. PubMed ID: 9220167. Immunological markers of disease progression in patients infected with the human immunodeficiency virus . Pascale J M; Isaacs M D; Contreras P; Gomez B; Lozano L; Austin E; De Martin M C; Gregory R L; McLaughlin G L; Amador A. (Department of Microbiology, Faculty of Medicine, University of Panama, Panama City.) CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, (1997 Jul) 4 (4) 474-7. Journal code: 9421292. ISSN: 1071-412X. Pub. country: United States. Language: English.

AB Identification of inexpensive and technically simple immunological tests useful in predicting the progression to AIDS in human immunodeficiency virus (HIV)-infected patients would be especially welcome in developing countries, in which 80% of

HIV-infected patients reside and health budgets are low. In the current study, we evaluated CD4+ and total lymphocyte counts and the concentrations in serum of beta 2-microglobulin, p24 antigen, and immunoglobulin A (IgA) as predictors of disease progression in 74 Panamanian HIV -positive patients and 50 HIV-negative healthy individuals. Total lymphocyte and CD4(+)-cell counts for AIDS patients (1,451 +/- 811 cells/microliters, P < 0.001, and 238 +/- 392 cells/microliters, P < 0.0001, respectively and asymptomatic patients (2,393 +/- 664 cells/microliters, P > 0.05, and 784 +/- 475 cells/microliters, P < 0.001, respectively) were lower than those observed for healthy subjects (2,596 +/- 631 cells/microliters and 1,120 +/- 296 cells/microliters, respectively). The levels of beta 2-microglobulin and IgA in serum were significantly elevated in patients with AIDS (5.7 +/- 3.6mg/liter, P < 0.001, and 541 +/- 265 mg/dl, P < 0.0002, respectively) and asymptomatic infected subjects (3.4 +/- 2.1 mg/liter, P = 0.001, and 436 +/- 216 mg/dl, P < 0.0001, respectively) compared with the levels in healthy subjects (2.2 +/- 0.7 mg/liter and 204 +/- 113 mg/dl, respectively). **Nonstatistically significant differences (P > 0.05) for concentrations of p24 antigen between asymptomatic infected patients (29 +/- 13 pg/ml) and AIDS patients (40 +/- 23 pg/ml) were observed.** Total lymphocyte counts of 1,750 cells/microliters or less, CD4 counts of 200 cells/microliters or less, beta 2-microglobulin concentrations in serum of 4 mg/liter or higher, concentrations of IgA in serum of 450 mg/dl or higher, and the presence in serum of p24 antigen were correlated with elevated risks for developing AIDS. Monitoring both total lymphocytes and beta 2-microglobulin identified 91% of the AIDS patients; these assays may allow reductions in the annual number of CD4(+)-cell evaluations and the costs associated with monitoring both total lymphocytes and beta 2-microglobulin identified 91% of the AIDS patients; these assays may allow reductions in the annual number of CD4(+)-cell evaluations and the costs associated with monitoring the immune status of HIV-positive patients.

L12 ANSWER 32 OF 83 MEDLINE

97125393 Document Number: 97125393. PubMed ID: 8970472. Virologic and serologic markers of rapid progression to AIDS after HIV-1 seroconversion. Farzadegan H; Henrard D R; Kleeberger C A; Schrager L; Kirby A J; Saah A J; Rinaldo C R Jr; O'Gorman M; Detels R; Taylor E; Phair J P; Margolick J B. (Department of Epidemiology, Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland 21205, USA.) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY, (1996 Dec 15) 13 (5) 448-55. Journal code: 9501482. ISSN: 1077-9450. Pub. country: United States. Language: English.

AB The association between early virologic and immunologic events after human immunodeficiency virus type 1 (HIV-1) infection and progression of HIV-1 infection to acquired immunodeficiency syndrome (AIDS) was studied among 59 homosexual men with documented time of seroconversion. Epidemiologic factors, such as number of lifetime sexual partners, history of sexually transmitted diseases, and other factors, also were studied. All 17 seroconverters in the cohort who developed AIDS within 3 years **(rapid progressors = RPs)** were compared with 42 men without AIDS for at least 6 years seroconversion **(nonrapid progressors = non-RPs)**. Plasma levels of HIV-1 RNA, p24 antigen, antibodies to HIV-1 structural genes, beta-2 microglobulin, neopterin, and interferon-alpha were measured at four time points: (a) the last seronegative visit, (b) the first seropositive visit, (c) the visit closest to AIDS (or the corresponding visit for the non-RPs) and (d) 6

years after seroconversion (for non-RPs). Up to seroconversion, the RPs had a significantly higher number of lifetime sexual partners than non-RPs (503 versus 171, respectively). At the first seropositive visit, **RPs had significantly higher concentrations of plasma HIV-1 RNA ($p < 0.01$) and prevalence of p24 antigenemia ($p < 0.001$)** and significantly lower levels of antibodies to the HIV-1 gag proteins p17 and p24 ($p < 0.01$-0.001) **compared with non-RPs**. These differences increased during follow-up visits. Antibodies to p66 and gp120 were significantly different only at the visit closet to AIDS ($p < 0.001$), as were beta-2 microglobulin and interferon alpha. These findings suggest that early virologic-immunologic events after HIV-1 infection may determine the rate of progression to AIDS. Anti-gag immune response may prevent rapid progression of HIV-1 disease and should be considered for future vaccine studies.

L12 ANSWER 39 OF 83 MEDLINE
96313021 Document Number: 96313021. PubMed ID: 8699074. Changes in virus load markers during AIDS-associated opportunistic diseases in human immunodeficiency virus-infected persons. Donovan R M; Bush C E; Markowitz N P; Baxa D M; Saravolatz L D. (Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan 48202, USA.) JOURNAL OF INFECTIOUS DISEASES, (1996 Aug) 174 (2) 401-3. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Human immunodeficiency virus (HIV) load markers are being used increasingly to monitor disease progression and evaluate antiretroviral therapy. This study examined plasma HIV RNA and p24 antigen levels before, during, and after 15 AIDS-associated opportunistic disease events in patients with AIDS (median CD4 cell count = 65/microL). Plasma HIV RNA was detected during 13 of the 15 events (median level before an event = 21,000 copies/mL). There was an increase in the level of plasma HIV RNA with the onset of an AIDS-associated opportunistic disease during 11 of 13 events for which HIV RNA was detectable (median level during an event = 145,000 copies/mL). There was a decline in the level of HIV RNA with the recovery from disease (median level after an event = 29,700 copies/mL). In contrast, **there was no consistent or significant change in p24 antigen levels or CD4 cell counts with either the onset of or recovery from an event**. Clinical interpretation of plasma HIV RNA changes must take into account this reversible elevation during AIDS-associated opportunistic disease.

L12 ANSWER 41 OF 83 MEDLINE
96260549 Document Number: 96260549. PubMed ID: 8697670. A decade of research on the natural history of HIV infection: Part 1. Markers. Strathdee S A; O'Shaughnessy M V; Montaner J S; Schechter M T. (British Columbia Centre for Excellence in HIV/AIDS.) CLINICAL AND INVESTIGATIVE MEDICINE. MEDECINE CLINIQUE ET EXPERIMENTALE, (1996 Apr) 19 (2) 111-20. Ref: 128. Journal code: 7804071. ISSN: 0147-958X. Pub. country: Canada. Language: English.

AB Within the context of HIV disease, **a marker may be described as a consequence of disease that varies over time but does not necessarily predict future disease course**. To date, the most powerful marker of HIV disease progression is the CD4 cell count. Other immunologic markers include neopterin, beta 2-microglobulin, and total and

HIV-specific immunoglobulin levels. Further research, which focuses on cell-mediated factors such as interleukins, tumour necrosis factor, natural killer cell activity and apoptosis, is required. Measures of viral burden, such as p24 antigenemia and proviral DNA or RNA, may also offer additional prognostic information. As methods involving quantitative polymerase chain reaction become more refined, it is hoped that they may soon be applied to the clinical setting. Clinical markers of interest include the appearance of minor opportunistic infections and the occurrence of acute retroviral syndrome, which may indicate a faster disease course. Although population-based studies have identified a number of HIV disease markers, further research is required to generalize these findings to the individual level.

L16 ANSWER 54 OF 56 MEDLINE
90231216 Document Number: 90231216. PubMed ID: 2184337. Antibodies to recombinant HIV-1 vif, tat, and nef proteins in human sera. Wieland U; Kuhn J E; Jassoy C; Rubsamen-Waigmann H; Wolber V; Braun R W. (Institut fur Medizinische Virologie, Universitat Heidelberg, Federal Republic of Germany.) MEDICAL MICROBIOLOGY AND IMMUNOLOGY, (1990) 179 (1) 1-11. Journal code: 0314524. ISSN: 0300-8584. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB The prevalence of antibodies against HIV-1 regulatory proteins in sera of HIV-infected patients from different stages of disease was investigated. HIV-1 vif, tat, and nef genes were cloned in procaryotic vectors and were expressed as MS-2 fusion proteins (vif and nef) or as a non-fusion protein (tat). These recombinant proteins were employed in immunoblot experiments. The specificity of the recognition was confirmed by competition experiments and with control sera from HIV-negative patients. Analysis of 136 serum samples revealed a high percentage of antibodies against nef, irrespective of the stage of disease. **Antibodies against tat were found less frequently and increased from 16% to 40% with disease progression**. Vif antibodies were detected only in a low percentage in early stages of disease, but their prevalence increased to 36% and 72% with progression of disease to AIDS-related complex and AIDS. Our data suggest that the detection of antibodies against nef may represent an additional and useful marker for the diagnosis of HIV infection, whereas the detection of vif antibodies may indicate disease progression.

L16 ANSWER 55 OF 56 MEDLINE
89080550 Document Number: 89080550. PubMed ID: 2462614. Natural antibodies to HIV-tat epitopes and expression of HIV-1 genes in vivo. Krone W J; Debouck C; Epstein L G; Heutink P; Meloen R; Goudsmit J. (Virology Department, University of Amsterdam, The Netherlands.) JOURNAL OF MEDICAL VIROLOGY, (1988 Nov) 26 (3) 261-70. Journal code: 7705876. ISSN: 0146-6615. Pub. country: United States. Language: English.

AB The tat regulatory protein of HIV-1 was expressed as a fusion protein in E. coli and used as antigen to detect antibodies against HIV-tat (anti-tat) in the serum of HIV -1 infected children and adults. HIV-1-infected children showed a higher frequency (55%) of anti-tat than HIV -1-infected adults (36%). Anti-tat were present in only 15% (3/20) of acutely infected individuals. Forty percent (10/25) of individuals with prolonged HIV-1 infection but without antigen were anti-tat positive. Only 13% (3/23) of HIV

-1-antibody-positive individuals with prolonged HIV-1 antigenemia were anti-tat positive and titers of anti-tat antibodies declined with time. Pepscan analysis identified the amino terminus of HIV-tat as the major antibody-binding site. Antibodies to HIV-tat occurred as a harbinger of HIV-1 antigen expression and disappeared thereafter, possibly reflecting the transience of HIV-tat expression. **Because of the low antigenicity of HIV-tat, antibodies to this regulatory protein are not a reliable marker for either early HIV-1 infection or subsequent disease progression.**

L16 ANSWER 56 OF 56 MEDLINE
87101492 Document Number: 87101492. PubMed ID: 3467797. Spectrum of natural antibodies against five HTLV-III antigens in infected individuals: correlation of antibody prevalence with clinical status. Franchini G; Robert-Guroff M; Aldovini A; Kan N C; Wong-Staal F. BLOOD, (1987 Feb) 69 (2) 437-41. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The genome of the HTLV-III/LAV retrovirus, the etiologic agent of the acquired immunodeficiency syndrome (AIDS), encodes the viral structural proteins (envelope and core proteins), the reverse transcriptase, a transactivation protein (tat-III), as well as two other proteins (3'orf, sor) of unknown function. We studied the prevalence of natural antibodies against envelope, gag, 3'orf, sor, and tat-III in the sera of HTLV-III infected individuals in an attempt to correlate clinical status with seropositivity to specific HTLV-III antigens. We selected 101 sera; 16 were obtained from normal donors with no known risk factors, and 85 were from patients with full-fledged AIDS (28 cases), AIDS-related complex (ARC, 22 cases), and healthy people at risk (homosexuals, intravenous [IV] drug users, relatives of AIDS patients; 35 cases). Seropositivity for antibodies against the envelope (gp41) and gag antigens (p15, p24) was determined by Western blot using disrupted HTLV-III virions. Of the 101 sera, all 16 from nonrisk donors and 3/35 from healthy at-risk donors were negative for antibodies against either the gp41 or p15 and p24. The remaining 82 sera were seropositive for either the gp41 and/or the p15 and p24. All sera were then tested against the three known HTLV-III antigens (3'orf, sor, and tat-III) that have been synthesized in bacteria. Our data indicate that all the HTLV-III antigens tested are immunogenic in vivo. No significant difference in antibody prevalence to gp41 (close to 100%) and to the 3'orf, sor, and tat-III proteins (approximately 50%) was observed with regard to stage of the disease. In contrast, the prevalence of antibodies against the core antigens decreased from approximately 100% in infected people with no clinical signs of disease to 50% in ARC and AIDS patients. The percentage of patients seropositive for all five antigens tested was increased in the AIDS group. These results indicate that the greatest antibody prevalence was obtained using viral envelope antigen and **further suggest that screening with the newly identified 3'orf, sor, and tat-III proteins as antigens would confer no further diagnostic advantage.** The pattern of natural antibodies observed during disease progression did not suggest any pathogenetic mechanism.

L17 ANSWER 4 OF 6 USPATFULL
2001:36426 Non-toxic immunogens derived from a retroviral regulatory protein antibodies preparation process and pharmaceutical compositions comprising them.
Zagury, Jean-Fran.cedilla.ois, Paris, France
Bizzini, Bernard, le Mesnil Saint Denis, France
Zagury, Daniel, Paris, France
Neovacs, Paris, France (non-U.S. corporation)
US 6200575 B1 20010313
APPLICATION: US 2000-570915 20000515 (9)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A non-toxic immunogenic compound, which may be administered to humans, is derived from an HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein by chemical processing using a coupling agent such as an aldehyde, or from a carrier protein activated by pre-processing using an aldehyde. This compound is capable of being recognized by antibodies to the viral regulatory protein and retains sufficient immunogenic properties to produce antibodies that neutralize or block the native protein, while losing at least 50% of the toxic biological properties of the native protein.

CLM What is claimed is:
1. A method for reducing the titer of a circulating native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein which is produced in a pathological viral condition, comprising causing a subject in need thereof to be immunized with a derivative of the native viral regulatory protein, which derivative is one which has lost at least 50% of a toxic biological property of the corresponding native viral regulatory protein and yet retains the capability of generating polyclonal antibodies cross-reactive with the corresponding said native viral regulatory protein.

2. A method in accordance with claim 1, wherein said loss of at least 50% of a toxic biological property is a loss of at least 50% of the property of immunosuppression of T cells, the property of deregulation is interferon-.alpha. production, the property of neoangiogensis, or the property of activation of CAT expression under the control of HIV-1 Long Terminal Repeat.

3. A method in accordance with claim 1, wherein said native viral regulatory protein is selected from the group consisting of the Nef, Tat, Vif and Rev regulatory protein of HIV-1 or HIV-2.

4. A method in accordance with claim 3, wherein said native viral regulatory protein is Tat.

5. A method in accordance with claim 4, wherein said loss of at least 50% of a toxic biological property is a loss of at least 50% of the property of immunosuppression of T cells, the property of deregulation of interferon-.alpha. production, the property of neoangiogenesis, or the property of activation of CAT expression under the control of HIV-1 Long Terminal Repeat.

6. A method in accordance with claim 1, wherein said derivative is the Tax regulatory protein of HTLV-1 or HTLV-2.

7. A method is accordance with claim 1, wherein said derivative has lost at least 80% of a toxic biological property of said native regulatory

protein.

8. A method in accordance with claim 1, wherein said derivative has lost at least 95% of a toxic biological property of said native viral regulatory protein.

9. A method in accordance with claim 1, wherein said derivative having modifications is a full length native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein having said modifications.

10. A method in accordance with claim 1, wherein said derivative comprises a fragment of the native viral regulatory protein.

11. A method in accordance with claim 10, wherein the native viral regulatory protein is Tat or Rev, and wherein said fragment is outside the basic region thereof or overlapping a basic region thereof by at most four amino acid residues.

12. A method in accordance with claim 1, wherein said derivative comprises all or a fragment of the native viral regulatory protein having modifications comprising deletions, substitutions or additions of the amino acid residues thereof, wherein less than 30% of the amino acids have been modified.

13. A method in accordance with claim 12, wherein less than 20% of the amino acids have been modified.

14. A method in accordance with claim 12, wherein less than 10% of the amino acids have been modified.

15. A method in accordance with claim 12, wherein said derivative having modifications is a fragment of a native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein, which fragment has said modifications.

16. A method in accordance with claim 1, wherein said derivative comprises all or a fragment of the native viral regulatory protein having chemical functionalization of the amino acid residues thereof.

17. A method in accordance with claim 16, wherein said derivatives having chemical functionalization is a full length native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein having said chemical functionalization.

18. A method in accordance with claim 16, wherein said derivative having chemical functionalization is a fragment of a native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein, which fragment has said chemical functionalization.

19. A method in accordance with claim 18, wherein said derivative comprises said fragment having chemical functionalization of the amino acid residues thereof by treatment with an aldehyde.

20. A method in accordance with claim 19, wherein said fragment is selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2.

21. A method in accordance with claim 16, wherein the chemical functionalization is other than that which causes conjugation to a carrier protein.

22. A method in accordance with claim 16, wherein said chemical functionalization is by acylation or treatment with an aldehyde or with

a coupling agent.

23. A method in accordance with claim 22, wherein said derivative comprises said native protein or fragment thereof having chemical functionalization of the amino acid residues thereof by treatment with a coupling agent so as to form an aggregate of the native protein.

24. A method in accordance with claim 23, wherein said coupling agent is glutaraldehyde.

25. A method in accordance with claim 22, wherein said derivative comprises said native protein or fragment thereof having chemical functionalization of the amino acid residues thereof by treatment with an aldehyde.

26. A method in accordance with claim 25, wherein said aldehyde is formaldehyde.

27. A method in accordance with claim 22, wherein said derivative comprises said native protein or fragment thereof having chemical functionalization of the amino acid residues thereof by acylation.

28. A method in accordance with claim 1, wherein said derivative comprises: (1) a fragment of the native viral regulatory protein; (2) all or a fragment of the native viral regulatory protein having modifications comprising deletions, substitutions or additions of the amino acid residues thereof, wherein less than 30% of the amino acids have been modified; or (3) all or a fragment of the native viral regulatory protein having chemical functionalization of the amino acid residues thereof.

L17 ANSWER 5 OF 6 USPATFULL
2000:137811 Non-Toxic immunogens derived from a retroviral regulatory protein, antibodies, preparation method therefor, and pharmaceutical compositions containing same.
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Bizzini, Bernard, Le Mesnil Saint Denis, France
Zagury, Daniel, Paris, France
NEOVACS, Paris, France (non-U.S. corporation)
US 6132721 20001017
WO 9627389 19960912
APPLICATION: US 1997-913221 19970908 (8)
WO 1996-FR357 19960307 19970908 PCT 371 date 19970908 PCT 102(e) date
PRIORITY: FR 1995-2708 19950308
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A non-toxic immunogenic compound, which may be administered to humans, is derived from an HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein by chemical processing using a coupling agent such as an aldehyde, or from a carrier protein activated by pre-processing using an aldehyde. This compound is capable of being recognized by antibodies to the viral regulatory protein and retains sufficient immunogenic properties to produce antibodies that neutralize or block the native protein, while losing at least 50% of the toxic biological properties of the native protein.

CLM What is claimed is:
1. An isolated modified protein comprising a derivative of a native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein, which

derivative comprises all or a fragment of the native regulatory protein having modifications comprising deletions, substitutions or additions of the amino acid residues thereof, and/or having chemical functionalization of the amino acid residues thereof by acylation or treatment with an aldehyde or with a coupling agent, said modifications and/or functionalizations causing said modified protein to lose at least 50% of the toxic biological properties of the corresponding said native viral regulatory protein and yet to retain the capability of generating polyclonal antibodies cross-reactive with the corresponding said native viral regulatory protein, wherein less than 30% of the amino acids have been modified, with the proviso that the functionalization does not cause conjugation to a carrier protein.

2. A modified protein in accordance with claim 1, wherein said derivative comprises said native protein or fragment thereof having chemical functionalization of the amino acid residues thereof by acylation or treatment with an aldehyde or with a coupling agent.

3. A process for preparing a modified protein in accordance with claim 2, comprising: chemically treating said native protein or fragment with an aldehyde or with a coupling agent, or to acylate amino acid residues thereof; and purifying the treated native protein or fragment.

4. A process in accordance with claim 3, wherein said chemically treating comprises chemically treating said native protein or fragment with an aldehyde.

5. The process in accordance with claim 4, wherein said aldehyde is formaldehyde.

6. The process in accordance with claim 4, further comprising treating the treated native protein or fragment with irradiation.

7. The process in accordance with claim 6, wherein the irradiation is UV irradiation.

8. A modified protein in accordance with claim 2, wherein said derivative comprises said native protein or fragment thereof having chemical functionalization of the amino acid residues thereof by acylation.

9. A modified protein in accordance with claim 2, wherein said derivative comprises said native protein or fragment thereof having chemical functionalization of the amino acid residues thereof by treatment with a coupling agent so as to form an aggregate of the native protein.

10. A modified protein in accordance with claim 9, wherein said coupling agent is glutaraldehyde.

11. A modified protein in accordance with claim 2, wherein said derivative comprises said native protein or fragment thereof having chemical functionalization of the amino acid residues thereof by treatment with an aldehyde.

12. A modified protein in accordance with claim 11, wherein said aldehyde is formaldehyde.

13. A modified protein in accordance with claim 1, wherein said derivative comprises said native protein or fragment thereof having modifications comprising deletions, substitutions or additions of the

amino acid residues thereof, wherein less than 30% of the amino acids have been modified.

14. A modified protein in accordance with claim 13, wherein less than 20% of the amino acids have been modified.

15. A modified protein in accordance with claim 13, wherein less than 10% of the amino acids have been modified.

16. A modified protein in accordance with claim 1, wherein said derivative is of a full length native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein.

17. A modified protein in accordance with claim 1, wherein said derivative is of a fragment of a native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein.

18. A modified protein in accordance with claim 17, wherein said derivative comprises said fragment having chemical functionalization of the amino acid residues thereof by treatment with an aldehyde.

19. A modified protein composition in accordance with claim 1, wherein said native protein is a viral regulatory protein selected from the group consisting of the Nef, Tat, Vif and Rev regulatory protein of HIV-1 or HIV-2.

20. A modified protein in accordance with claim 19, wherein said viral regulatory protein is Tat.

21. The modified protein in accordance with claim 1, wherein said modified protein is the Tax regulatory protein of HTLV-1 or HTLV-2.

22. The modified protein in accordance with claim 1, wherein the toxic biological properties are immunosuppression of T cells, deregulation of interferon-.alpha. production, or neoangiogenesis.

23. The modified protein in accordance with claim 1, wherein the modified protein has lost at least 80% of the toxic biological properties of said native viral regulatory protein.

24. The modified protein in accordance with claim 1, wherein the modified protein has lost at least 95% of the toxic biological properties of said native viral regulatory protein.

25. An immunogenic composition, comprising, as active ingredient, a derivative of a native HIV-1, HIV-2, HTLV-1 or HTLV-2 viral regulatory protein, which derivative comprises all or a fragment of the native regulatory protein, having modifications comprising deletions, substitutions or additions of the amino acid residues thereof, and/or having chemical functionalization of the amino acid residues thereof, said modifications and/or functionalizations causing said modified protein to lose at least 50% of the toxic biological properties of said native viral regulatory protein and yet to retain the capability of generating polyclonal antibodies cross-reactive with said native viral regulatory protein, wherein less than 30% of the amino acids have been modified, with the proviso that the functionalization does not cause conjugation to a carrier protein, and a pharmaceutically acceptable adjuvant.

26. The immunogenic composition in accordance with claim 1, further comprising an immunogenic compound in association with the modified

protein.

27. The immunogenic composition in accordance with claim 26, wherein said immunogenic compound is selected from the group consisting of tetanic toxoid, gp120 or gp160 protein which is native or inactivated by physical, chemical, genetic or immunological treatment, and an immunogenic fragment of said gp120/gp160 protein.

L24 ANSWER 5 OF 9 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-224721 [19] WPIDS
DNN N2000-168310 DNC C2000-068782
TI Prognosis of human immune deficiency virus infection, used e.g. to assess suitability for vaccination, based on levels of serum markers, particularly anti-tat antibody.
DC B04 D16 S03
IN ZAGURY, D; ZAGURY, J
PA (MCIN-I) MCINNIS P A; (NEOV-N) NEOVACS
CYC 21
PI WO 2000011225 A1 20000302 (200019)* EN 49p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: SD US
EP 1123419 A1 20010816 (200147) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 2000011225 A1 WO 1999-US18770 19990820; EP 1123419 A1 EP 1999-945084 19990820, WO 1999-US18770 19990820
FDT EP 1123419 A1 Based on WO 200011225
PRAI US 1998-97497P 19980821

AB WO 200011225 A UPAB: 20000419
NOVELTY - Determining the prognosis of an HIV (human immune deficiency virus)-infected subject comprises comparing the levels, in the serum, of at least one marker (I) with levels that are indicative of disease progression or non-progression. (I) is anti-tat antibody (Ab), tat protein or p24 protein.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) treatment of HIV infection by measuring the level of Ab or tat protein over time and administering a tat vaccine (to increase levels of Ab) if either a sufficient decrease in Ab or sufficient increase in tat is detected; and

(2) evaluating the immune response of an uninfected subject to tat vaccine by measuring serum levels of Ab or tat before immunization and then after immunization as a measure of humoral immune response.

ACTIVITY - Anti-HIV.

MECHANISM OF ACTION - Vaccine. Induction of a specific immune response, which may overcome tat-induced immunosuppression and viral dissemination, allowing the immune system to respond successfully to HIV-1 infection. Inactivated tat protein was used to immunize seropositive but asymptomatic subjects, by intramuscular injection. The priming dose was 0.1 mg, with boosters of 50 mu g given until the level of anti-tat antibodies (Ab) had at least doubled (median of 3 injections needed). Ab levels increased 2-8 fold, including in patients receiving anti-retroviral drugs and/or interferon alpha . Of 8 subjects tested, four showed a delayed hypersensitivity response to intradermal immunogen, and four of six showed a cell-mediated immune response. The vaccine was well tolerated and in some subjects caused (i) an increase in absolute levels of CD4+ cells and/or (ii) a reduction in levels of HIV-1 and p24 antigen. None of the vaccinated subjects showed an increase in virological parameters during the follow-up period.

USE - The new method is used to detect progression of HIV infection to AIDS (acquired immune deficiency syndrome). Detection of Ab is also used to identify subjects who might benefit from administration of anti-tat vaccine and to evaluate the immune response to such a vaccine, which can be used to treat or prevent infection.

ADVANTAGE - Tat, Ab and p24 are good predictors of disease progression, at least in the early stages. A prior art marker, such as viral load, is low at the early stages of the disease while a test with p24 protein alone is only used to determine whether an individual is

affected, not as a prognostic indicator of disease progression.
Dwg.0/5